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COMMENTARY

Residual Attributable Mortality, a New Concept for Understanding the Value of Antibiotics in Treating Life-Threatening Acute Infections[▽]

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Crude mortality has been a longstanding measure of the outcome of severe acute infections. Nevertheless, it has been recognized that this outcome in populations is the sum of the effect of the patients' underlying diseases plus the effect of the infections. The term attributable mortality is an epidemiological measure of the direct contribution of the infections after accounting for the contribution of the underlying diseases (14). Historical cohort studies in which individual case patients are tightly matched to one or more uninfected controls are well suited to estimate attributable mortality (3, 5, 6, 7, 15). It is important to emphasize that the matching process is critical to achieve accurate results, and this is a challenging aspect of study design. Specifically both primary and all secondary diagnoses and recent surgical procedures would be equivalent in case patients and controls, and controls should be in the hospital at least as long as the interval between admission and infection in the case patients (another surrogate for underlying illnesses). Importantly, across several studies performed over extended time periods, there has been a great variation in these estimates, sometimes leading to arguments that focus on study design. Specifically, where matching has been imprecise, attributable mortally has been over estimated.

The hypothesis of this concept paper is that changes in the effective use of antibiotics can explain some of the variations noted in presumed attributable mortality for bloodstream infections. The purpose of this paper is to offer definitions for attributable mortality and introduce the concept of residual attributable mortality, which together will be useful both in understanding the impact of antibiotics on patient outcomes and in designing clinical studies of new interventions for infectious diseases.

ATTRIBUTABLE MORTALITY

In its simplest form, we would define attributable mortality as the direct contribution to death from infections after accounting for underlying illnesses and assuming no effective therapy (Fig. 1). It is emphasized that this is an epidemiological term applied to populations, not a clinical one, since each case patient is tightly matched to one or more controls—essentially a series of twins except for the infection in the case patients. Those who suggest that they have estimated attributable mortality by expert clinicians' reviews of the charts fail to appreciate that such an approach uses as controls the vague clinical impressions of what might have happened in the absence of an infection. There is essentially no reproducible discipline employed.

Since the case patients received no therapy, the attributable mortality defines the optimal effect of an intervention such as an effective antibiotic (14). For example, if case patients have a crude mortality of 40% and if tightly matched controls have a crude mortality of 20%, the attributable mortality of 20% defines the maximal potential impact of an intervention. If a "perfect" antibiotic were employed to treat the case patients, the crude mortality would not fall below the 20% crude mortality of uninfected case patients—essentially the mortality of the underlying diseases, which is not influenced by antibiotic treatment.

Some epidemiologists and statisticians may view the favorable effect of an antibiotic noted in a clinical trial as an issue of cause and effect, in which the effect is defined only in comparison to the outcome of controls. The effect size can be measured as the absolute difference in mortality or the proportional difference. For example, such comparative effects are referred to as counterfactual models of causation (4). The idea is that if one removes the (same) underlying diseases in the case patients and controls the difference reflects the effect of the antibiotic.

RESIDUAL ATTRIBUTABLE MORTALITY

An important point is that as better and better antibiotics are successively employed over time to treat specific infections, the crude mortality of case patients will fall and approach the mortality of the matched controls because the impact of infections falls. We suggest that the term residual attributable mortality be used to define what is remaining of the original attributable mortality in the era of increasingly effective antibiotics. Note that as one approaches the ideal or perfect antibiotic, the residual attributable mortality approaches zero (Fig. 2).

A current misconception in the era of increasingly effective antibiotics is made by those who incorrectly describe "low attributable" mortality for the more precise term, residual attributable mortality. This could have serious treatment implications. The idea of a very low attributable mortality implies that there is little need for antibiotics. A key concept, however, is that even if the residual attributable mortality approaches

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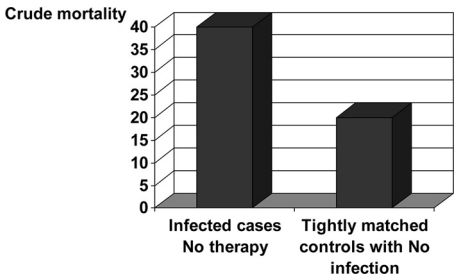

FIG. 1. Crude mortality of infected case patients given no therapy and of tightly matched controls. Theoretical outcome of infections having a crude mortality of 40% in the absence of therapy. Since matched controls had a crude mortality of 20%, the estimate of attributable mortality is 20% (40% − 20%). Since the case patients received no effective therapy for the infection, the 20% attributable mortality defines the maximum benefit of a completely effective intervention such as an excellent antibiotic. This is true if we assume that an intervention for infection would not reduce the mortality due to the underlying diseases.

zero because of the impact of an almost perfect antibiotic, effective antibiotics would still be needed to treat the underlying true attributable mortality. If one withdrew antibiotics, the crude mortality would rise incrementally to a level consistent with the contribution of the original attributable mortality.

From the above discussion, it is now understandable that earlier studies of "attributable mortality" would have higher estimates than later studies. In fact, the later studies actually estimated the residual attributable mortality in the face of effective therapy. It is then reasonable to consider the two major predictors of residual attributable mortality: (i) concordant therapy (the organism is susceptible to the drug administered) and (ii) "early" administration of the antibiotic, currently—and somewhat arbitrarily—defined as within 24 h of the onset (or recognition) of the infection.

In theory, the residual attributable mortality could increase or decrease as a result of a third factor—the virulence of a species. If a species were to change or if a specific genus lost or acquired virulence factors, the crude and residual attributable mortality could change. Virulence is often independent of the organism's antibiotic susceptibility profile, however.

PERSPECTIVE FROM THE LITERATURE

A perspective from the literature focuses on *Candida* bloodstream infections. There are three lines of evidence that *Candida* bloodstream infections carry a substantial attributable mortality: models in which *Candida* is an independent predictor of mortality (9, 12), historical cohort studies showing significant attributable mortality (5, 15), and studies showing the lifesaving value of early versus delayed institution of therapy (10, 11).

At one time, however, it was uncertain if *Candida* independently contributed to mortality in bloodstream infections. In a 1974 paper by Stone et al. describing 58 cases of *Candida* sepsis occurring between 1963 and 1973, 32 patients died (55%). Of interest, no therapy was given to 14, and an additional 23 received only oral nystatin. Only 16 received amphotericin B. (13).

No attempt at matching underlying illnesses was made, and thus, crude mortality percentages only were reported for 14 patients who received no therapy and were diagnosed at autopsy (100%), 5 patients in whom intravenous "feeding" was discontinued but no therapy was given (20%), 23 who received oral nystatin alone (26%), 9 who received intravenous amphotericin only (78%), and 7 who received both nystatin and amphotericin (57%) (10).

In a discussion of therapy, the authors stated that "Because fungi that have already invaded rarely survive for any period of time within the host with a reasonably normal reticuloendothelial system, the value of parenterally administered agents does not appear as significant as once believed." It was incorrectly assumed that the crude mortality of 55% was due solely or almost solely to the underlying diseases. In fact, most of the crude mortality was attributable to serious, untreated infections.

Even 20 years later, in a 1994 editorial warning of the direct impact of candidemia, Meunier captured the sentiment of experienced clinicians regarding *Candida* bloodstream infections: "For too long, candidemia in patients without neutrope-

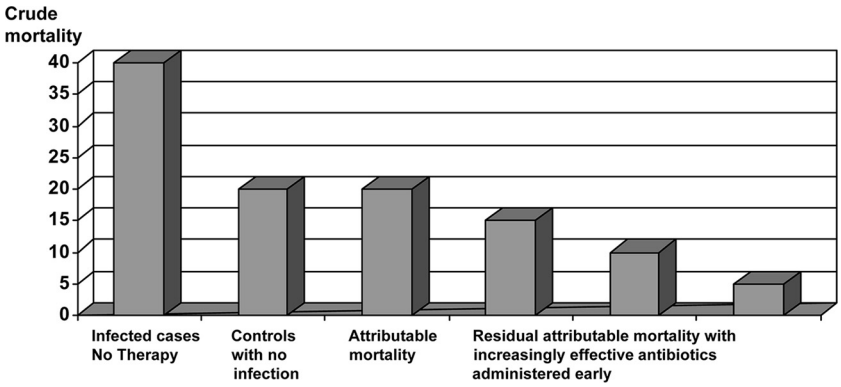

FIG. 2. Crude mortality of infected case patients and tightly matched controls in the era of increasingly effective therapy. Assume that infected case patients have a crude mortality of 40% and tightly matched controls have a crude mortality of 20%. The attributable mortality is thus 20% (40% − 20%). With an infection that has an attributable mortality of 20% with no effective therapy, the theoretical residual mortality for increasingly effective antibiotics is shown. An antibiotic that reduces the attributable mortality by an absolute difference of 5% would result in a residual attributable mortality of 15%. One could also say that the same antibiotic reduced the attributable mortality by 25% (5%/20%). The example shows decreasing residual attributable mortalities of 15%, 10%, and 5% as an increasingly effective therapy reduced the attributable mortality by absolute differences of 5%, 10%, and 15%, respectively.

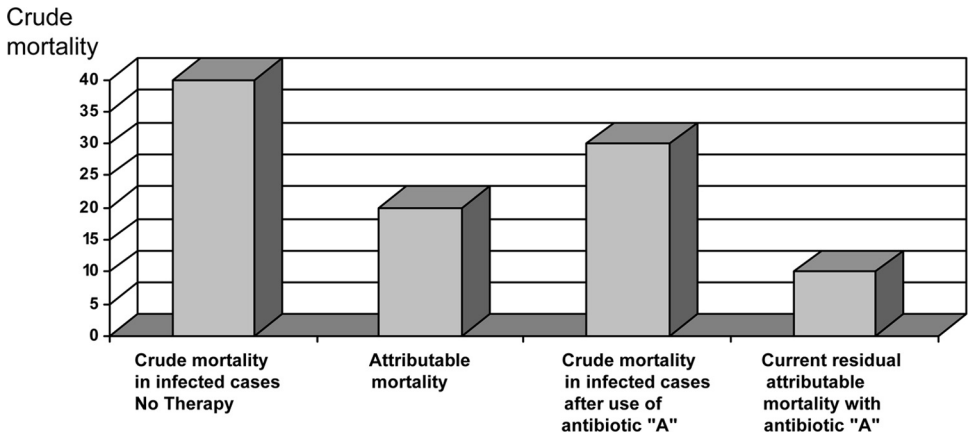

FIG. 3. Residual attributable mortality after treatment with drug A. Assume a crude mortality of 40% in infected case patients receiving no therapy and a 20% crude mortality among tightly matched controls. The resulting 20% attributable mortality is the estimate of how much a perfect antibiotic will affect outcome. If a partially effective antibiotic can reduce the attributable mortality by an absolute value of 10%, this will reduce the crude mortality from 40% to 30%, leaving a residual attributable mortality of 10%.

nia has been considered a transient benign phenomenon that does not require treatment" (8). However, in one of the earliest studies to challenge this concept, that candida contributed little to crude mortality, Miller and Wenzel modeled risk factors of death after nosocomial bloodstream infections and showed that the isolation of *Candida* species was an independent predictor of mortality (9). These data were later confirmed in models at a different university, where *Candida* was identified as the only organism independently predicting mortality among patients with bloodstream infections (12). Furthermore, Wey et al. and Gudlaugsson et al. showed substantial estimates of attributable mortality—38% and 49%, respectively—at the same institution for over a decade, after performing historical cohort studies (5, 15). Importantly, when Wey et al. did their study, a substantial number of patients were not treated or were treated only after several days of delay after a positive culture was obtained. In the study by Gudlaugsson et al., 15 patients were not treated, a situation that greatly influenced the attributable and thus the crude mortality: 12 of 15 nontreated case patients died (5).

In recent studies, early therapy of *Candida* bloodstream infections was shown to predict a more favorable outcome. In children, Pacheco-Ríos et al. showed that the risk of death after candidemia increased significantly for each day of delay in treatment (11). In adults, Morrell et al. showed that in candidemia, the administration of antifungal therapy 12 h after having the first positive blood culture versus treating within 12 h had an adjusted odds ratio of 2 for predicating hospital mortality (10). In a matched-cohort study, Blot and colleagues showed that the mortality from candidemia was 78% in those in whom antifungal therapy was delayed >48 h versus 44% if it was given within 48 h of the onset of candidemia (1). The weight of the evidence clearly shows substantial attributable mortality with *Candida* bloodstream infections.

Recently, study designs have changed. For example, Blot et al. matched patients with APACHE-2 scores and case patients were treated a median of 1 day from the onset of candidemia (1). Not only was there early treatment, but also all colonized patients were given "preemptive" antifungal therapy when they developed fever. Since two-thirds of the patients with candidemia had preceding colonization, it is likely that early therapy plus preemptive antibiotic use greatly influenced mortality in that population of patients (1). The study design required that all case patients were treated, and all case patients are given therapy early, a situation that would maximize therapy and lead to a low residual attributable mortality. Although the authors used the term "attributable mortality," they in fact estimated a residual attributable mortality of 5% in the face of currently effective preemptive therapy plus early treatment of infections with antifungals.

IMPLICATIONS FOR STUDY DESIGN

The concept of residual attributable mortality is essential for proper study design of clinical trials comparing two antibiotics. To return to an example, assume that the crude and attributable mortalities for specific bloodstream infections in case patients and controls were 40% and 20%, respectively. However, with effective therapy (antibiotic A) leading to a residual attributable mortality of 10%, the crude mortality would fall from 40% to 30% (Fig. 3).

If a promising new antibiotic, B, is thought to be much better than A, how does one size the study to achieve an 80% power to show a 20% proportionately better mortality outcome? It might be tempting in a superiority trial to seek the number required in each study arm by comparing the 30% and 24% crude mortality data (an absolute 6% difference from a crude mortality of 30% and a relative difference of 20%). However, the true approach would need to consider the difference only in residual attributable mortality of 10% versus 8% (also a 20% relative decline). Note that the antibiotic would have an effect only on the residual attributable mortality component. In the latter example, one would be examining the difference in crude mortality of 30% versus 28%—an absolute difference of only 2%!

Assume that a superiority trial is planned with alpha set at 5%, with power at 80%, and with a one-sided *P* value employed. If one calculates the number of study subjects needed only by looking at the expected new crude mortality—24%,

TABLE 1. Examining the importance of study design with the help of residual attributable mortality estimates in a superiority trial[a]

Total crude mortality				Residual attributable mortality		
Drug A (%)	Assuming drug B better by proportion (%)	Expected new value for drug B (%)	No. of study subjects/arm	Expected new crude value for drug B (%)	No. of study subjects/arm	Power (%) using sample size in column 4
30	20	24	709	28	6,464	19
30	30	21	311	27	2,865	18
30	40	18	172	26	1,607	17
30	50	15	108	25	1,025	16

[a] Assume a superiority trial design with 80% power, an alpha of 5%, and a one-sided *P* value in a superiority trial assuming a 10% maximal impact of drug B, i.e., attributable mortality. Calculations were conducted using nQuery 7.0.

21%, 18%, or 15%—then the number of study subjects in each arm will only be as high as 709 to as low as 108 (Table 1) The expected new crude mortality data correspond to a proportional 20%, 30%, 40%, or 50% decrease in crude mortality. However, since the drugs for infection will affect only the residual attributable mortality, the expected new crude mortality with drug B will accurately be predicted to be 28%, 27%, 26%, or 25%, respectively. Now the number of study subjects needed will vary from as many as 6,464 to as few as 1,025 per arm (Table 1). By understanding the importance of residual attributable mortality, those planning the study will know that the true number of study subjects needed for appropriate power will be 10 times more than if only crude mortality were used to size the study. Note that if one considers only crude mortality, the low number of subjects in each study arm causes a desired power of 80% to fall to 16 to 19% (Table 1, far right column). Not only will an increased sample size be an issue, but also estimating the crude mortality of controls will be challenging, especially since the small decreases in case patients mortality may not be considered clinically relevant.

In an example with a noninferiority trial (2) (Table 2), one can see that failure to examine residual attributable mortality also underestimates the number of subjects needed in each study arm, but much less so than in a superiority trial. Nevertheless, examining the far right column, one can see that examining only crude mortality with fewer subjects than needed will reduce study power from a desired 80% to an actual 74% to 56%.

It would be especially interesting in examining clinical trials of two alternative antibiotics to measure the residual attributable mortality of each arm of the study. The two antibiotics could then be compared not only with respect to differences in crude mortality but also with respect to differences in residual attributable mortality after correcting for the contributions of the underlying diseases. We would quickly acknowledge the enormous challenges in completing such time-consuming analyses, however.

If the clinical trial showed a crude mortality of 30% with drug A and 20% with drug B, it would be tempting to conclude only that drug B improved the outcome by 33% (relative difference) or 10% (absolute difference). However, the crude mortalities of 30% and 20% are the sums of underlying diseases and residual attributable mortalities. Furthermore, the subjects in each arm may not be tightly matched for underlying diseases, even though confounding is minimized by randomization.

In the example above, if we knew that the mortality from underlying diseases was 15% for those given drug A and 18% for those given drug B, we could say that the residual attributable mortality was 15% for drug A and 2% for drug B. The difference in residual attributable mortality estimates would then be 15% − 2% or 13% (Fig. 4). In this example, the difference in residual attributable mortality is more enlightening than one might have estimated from the crude data. To know this, however, one would have to perform the clinical trial and then do two excellent historical cohort studies, one for each arm of the study.

WILL MODELING RESIDUAL ATTRIBUTABLE MORTALITY BE MORE EFFICIENT?

The performance of historical cohort studies in which each infected case patient is tightly matched to one or more uninfected, "twin" controls is tedious work, requiring a great deal of time identifying the best match for each case patient. The degree of matching defines the rigor of the study. So an im-

TABLE 2. Examining the importance of study design with the help of residual attributable mortality estimates in a noninferiority trial[a]

Total crude mortality				Residual attributable mortality		
Background (%)	Assuming improvement from background with either drug A or B (%)	Expected new value for both drugs (%)	No. of study subjects/arm	Expected new crude mortality with both drugs (%)	No. of study subjects/arm	Power (%) using sample size in column 4
30	20	24	390	28	425	74
30	30	21	359	27	420	67
30	40	18	320	26	405	64
30	50	15	280	25	398	56

[a] Assume a noninferiority trial design (drug A is the standard treatment; drug B is generic) with 80% power using a two-sided 95% confidence interval with a margin of noninferiority of 10% (i.e., the confidence interval on the difference between the mortality rates in the two arms is contained within −0.10, 0.10) in a trial assuming a 10% maximal impact. Calculations were conducted using nQuery 7.0.

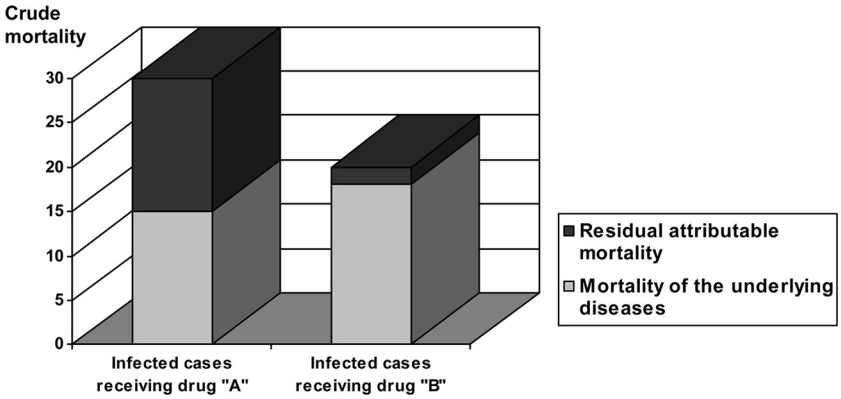

FIG. 4. Comparing residual attributable mortalities after treatment with drug A versus drug B. The crude mortality data are shown for a hypothetical clinical trial in which antibiotic A is compared to antibiotic B. Crude mortality was 30% with antibiotic A and 20% with antibiotic B. The absolute difference (crude) is 30% − 20% = 10%. More insight could be gained, however, by examining the difference in residual mortality. In this example, the residual attributable mortality with drug A is 15% whereas with drug B the residual attributable mortality is only 2%—an almost perfect antibiotic. The difference in residual attributable mortality is 15% − 2% = 13%.

portant question is whether with computational help a model can perform the matching in a more efficient manner.

One exciting possibility has already been explored by Zaoutis et al., who used a "propensity analysis" to examine outcomes attributed to candidemia. In brief, the authors examined a large number of variables that would be expected to predict candidemia and then estimated the probability of candidemia utilizing multivariable logistic regression (12). For each case patient, there were two controls with very closely matched propensity scores—one control with a score just above and one with a score just below that of the case patient. If close scores could not be found for controls to a specific case patient, the latter case-control set was excluded. Zaoutis and colleagues were able to show remarkable discrimination between case patients and controls and subsequently identify differences in mortality (12). In 2000, he and his colleagues measured a 14.5% residual attributable mortality of adults with candidemia by using propensity analysis. This approach might be useful in estimating the residual attributable mortality in a clinical trial comparing alternative treatment arms.

CONCLUSIONS

It is proposed that the term residual attributable mortality has value in understanding the successive improvement in outcomes with better interventions for severe acute infections. It is distinguished from attributable mortality, which we would define as the best estimate of direct outcome from acute infections with totally ineffective interventions or no therapy. Clinicians need to know that even with an eventual residual attributable mortality of zero percent, patients would need antibiotics to treat the original underlying attributable mortality of the life-threatening infections. It is likely that the variations in "attributable mortality" in studies performed over decades of time can be explained in part by understanding the changes in residual attributable mortality as a result of concordant therapy administered earlier in the infections. Understanding residual attributable mortality is essential for appropriate study design of clinical trials comparing two alternative antibiotics.

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